A Novel Alternative Approach for Prediction of Radiation Response of Squamous Cell Carcinoma of Head and Neck

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Abstract

Accurate prediction of human tumor response to radiation therapy and concomitant chemoradiation would be an important tool to assist the physician in making recommendations for tumor treatment. Most of the studies that define the molecular markers for prediction of radiation response are based on the observation of gene expression using immunostaining, Northern blot, or Western blot analysis of a single or several genes. The results vary among different studies, and some results are contradictory. However, the studies agree that the change in expression of the tumor-related gene affects the radiation response. In this study, we explored a novel approach to predict the radiation response of human tumor using Atlas human cancer 1.2 cDNA array to analyze the expression profile of 1187 tumor-related genes in radiation-resistant and radiation-sensitive tissues. Sixty tumor-related genes were selected as predictors of radiation response of squamous cell carcinoma of the head and neck. Using the expression intensity of these 60 tumor-related genes, in combination with cluster analysis, we successfully predicted the radiation identity of two tumor samples.

Introduction

SCC of the upper aerodigestive tract has excellent control rates with either surgery or radiation, if diagnosed in its early stages. However, SCCHN has a significantly high rate of death when the cancer presents in an advanced stage, despite the development of a number of different, aggressive, and multimodal treatments. Reported 5-year survival rates vary from 38 to 60% (1–4). Recently, treatment protocols evoking organ preservation by using concomitant chemoradiotherapy have appeared in the literature as an alternative therapy to avoid this morbidity. Despite the high general success of this treatment, patients who fail to benefit from this treatment require a more difficult surgery. Thus, a prognostic molecular marker would be useful for predicting the outcome of the concomitant chemoradiotherapy.

Expression of certain oncogenes and/or inactivation of tumor suppressor genes as well as apoptosis and cell cycle genes may alter the cellular radiation responses, based on in vitro cell culture study and in vivo preclinical and clinical studies (5–9). In general, transfection of transforming oncogenes in vitro increases cellular radiosensitivity (5–9). Increased endogenous oncogene expression has also demonstrated radiation resistance in tumor cell lines and tissues. High levels of epidermal growth factor receptor, c-myc, and Ki67 expression increased radiation resistance of SCCHN (10). Increased c-ras expression implicates the radioresistance of SCCHN (11). Overexpression of c-jun and c-H-ras correlates to radioresistance of clinical laryngeal tumor samples (12).

Apoptosis is considered a major molecular mechanism of radiation-induced cell killing of reticular epithelial tumors. Overexpression of apoptotic suppressing genes or down-regulation of proapoptotic genes can potentially render tumor cells radioresistant (13). The most widely studied genes for radiation response are the ones from the bcl-2 family. Overexpression of bcl-2 in multiple tumor cells (13–15) increases radiation resistance, and bax, the other member of the bcl-2 family, antagonizes the bcl-2 function by forming a heterodimer. The predictive value of bcl-2 for radiation resistance has been examined in breast cancer, prostate cancer, and head and neck cancer (15–17). There are also results suggesting no association between bcl-2 expression and tumor radiosensitivity (18, 19).

Several other cell cycle genes and other functional genes may also participate in the regulation of radioresistance. Glutathione S-transferase-P may predict irradiation resistance in SCCHN (20). Tumor suppressor gene p21 expression was correlated to the sensitivity of rectal cancer to radiation (18); p53-negative and p21-positive staining in tissue samples from rectal cancer patients correlated with the responses of the cancers to radiation (21). Some studies found a significant correlation between p53 immunostaining and rectal cancer radiosensitivity (18, 22), but others were unable to confirm these findings (19).

In summary, radiation resistance is determined by multiple cellular events that are controlled by a large pool of genes and their interactions; thus, it is critical to compare the expression of these markers simultaneously. Molecular cDNA array is a unique tool for such a comparison. In this report, we have simultaneously analyzed 1187 cancer-related genes with a cDNA array technique that may contribute to the radiation resistance in SCCHN, and we have introduced a mathematical method for the prediction of radiation resistance from tumor gene-expression profiles.

Materials and Methods

RNA Isolation from Biopsy and Surgical Samples. SCC biopsy and surgical tissues were obtained from patients undergoing surgical resection at the University of Arkansas for Medical Sciences, with the protocol approved by the University of Arkansas for Medical Sciences institutional review board. After surgical removal, samples were immediately snap-frozen in liquid nitrogen. Tumor tissues were homogenized in TRIZol reagent (Life Technologies, Inc., Rockville, MD) with a bead-beater to extract total RNA (23).

Atlas cDNA Array Analysis. RNA (30 μg), was treated with 10 units of DNase I (MessageClean kit; GenHunter Corp., Nashville, TN) for 30 min at 37°C to digest any contaminating DNA. Three μg of total RNA from each sample were converted into 32P-labeled first-strand cDNA by reverse transcription using gene-specific primers, according to the manufacturer’s specifications (Clontech Laboratories, Inc.). Probes were purified and hybridized to the filter array overnight at 68°C. Filters were washed and exposed to a Storage phosphor screen (Molecular Dynamics, Sunnyvale, CA), and differences in the signals among samples were scanned by a PhosphorImager analyzer (Model...
445 SI; Molecular Dynamics) and analyzed by Atlas Image 1.5 software (Clontech). For normalization, the most consistent results have been obtained by choosing a global method. The filters hybridized from sensitive and resistant probes were exposed in a manner such that a similar signal intensity was produced from both filters. The filters containing 1187 unique human cancer-related genes are available from Clontech.

Cluster Analysis. If the ratio of gene expression between the radiation sensitive and resistant tumor tissues changed >3-fold and/or the absolute difference was >75, then the gene was selected for cluster analysis after the transformation of raw observation (adjusted intensity) using the equation: $y = \log_{10}(x + 1)$, where $x$ equals the adjusted intensity from array analysis, and $y$ is the transformed adjusted intensity. The cluster analysis was performed using weighted pair-group average and Euclidean distance available in the software STATISTICA (StatSoft, Tulsa, OK). A tree diagram was generated by the software.

Results

Differential Expression of Tumor-related Genes from Radiation-sensitive and Radiation-resistant Samples. We hypothesize that a change in the whole profile of tumor-associated gene expression, not a single gene, will determine the tumor response to radiation. This hypothesis suggests that changes in gene expression will affect the radiation response. Thus, a large group of genes may give a better prediction of radiation response. To test this hypothesis, two biopsy samples from radiation-sensitive tumors and two from radiation-resistant tumors were subjected to gene expression analysis using the Atlas human cancer 1.2 CDNA array. The radiation-sensitive tumor was defined as no evidence of tumor, whereas radiation-resistant tumor was defined as <40% decrease in tumor size at the end of 6 weeks of treatment with a total 68–70 Gy. This array filter contains 1187 tumor-related genes, including oncogenes, tumor suppressor genes, cell cycle genes, and apoptosis genes. As shown in Fig. 1, some gene expression was higher and, in other genes, expression was lower in radiation-resistant tumor tissues compared with radiation-sensitive tissue. Such a gene expression profile may vary among the resistant or sensitive individuals. To include the majority of the prognostic genes, all four patient samples were included for gene-expression analysis.

To determine the genes overexpressed in radiation-resistant or radiation-sensitive tumor tissues, genes that demonstrated an expression ratio of >3-fold or an absolute difference (when the ratio cannot be defined) of 75 in expression from radiation-resistant and radiation-sensitive tissues were subjected to cluster analysis. This method was more reliable than examining the 1187 genes from four patient samples visually. Prior to the cluster analysis, the gene-expression values (adjusted intensity) of the selected genes (60 genes) were averaged within radiation-resistant or radiation-sensitive individual samples. Then, the averaged adjusted intensity of each selected gene was transformed using the equation (see “Materials and Methods”). Such a transformation was to avoid bias by a single high value and to ensure the consideration of both the ratio and the absolute difference in the cluster analysis. During the data transformation, $x + 1$ was used instead of $x$ itself for the mathematics. As Fig. 2 shows, three groups were clustered. The right group was composed of genes with a higher
level of gene expression in radiation-resistant tissue, the middle group was formed from genes with >3-fold expression in the sensitive tissue, and the left group represents genes with high levels of expression in radiation-sensitive tumors but not detectable expression levels in radiation-resistant tissue. Summaries of radiation-resistant and -sensitive genes determined in this study are listed in Tables 1 and 2, respectively.

Prediction of Radiation Response by Cluster Analysis Using 60 Selected Genes. To further determine whether such selected gene-expression profiles from radiation-sensitive and radiation-resistant groups can predict the radiation response of the tested tumor sample, the gene-expression profile was determined from two samples using the same array filter and method in a single blind approach. These two samples were known to be radiation sensitive based on the clinical response as described above. After gene probe hybridization and scanning analysis, the adjusted intensity of the 60 genes was determined and transformed. Then, the transformed intensity was clustered with the known sensitive and resistant groups described above using the 60 selected gene-expression profiles to determine the initial cluster group. The linkage distance, Euclidean distances, was calculated

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<th>Ave R2</th>
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<th>Difference Protein/gene</th>
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* The ratio cannot be determined.

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* The ratio cannot be determined.
two samples, the more similar was the radiation response. As ex-
in “Materials and Methods.” The shorter the linkage distance between
between each pair based on the gene expression profile as described
in “Materials and Methods.” The shorter the linkage distance between
two samples, the more similar was the radiation response. As ex-
pected, this radiation-sensitive sample had a much shorter cluster
linkage (Euclidian) distance than the radiation-resistant sample and
was clustered with the radiation-sensitive group first (Fig. 3A).

Similarly, another radiation-sensitive tumor sample was tested and clus-
tered with the sensitive group first (Fig. 3B). This suggests that such
an approach will be meaningful for radiation prediction.

Discussion

The prediction of radiation response is a critical step to determine
the treatment strategy and reduce potential patient suffering. It has
been known that many cancer-related genes may involve and could
predict the radiation response, but the prediction using a single gene
may not be accurate and may be contradictory (5–22) in many cases.
Thus, a large number of genes were used in this study for prediction of
the outcome of radiation response. To analyze this large number of
genomes simultaneously, a relatively novel technology, cDNA array, was
used. The cDNA and oligonucleotide-based microarray technology
has become a method of choice for many applications, including
identifying disease-related genes and treatment-responsive genes and
determining carcinogenicity, toxicity, and drug safety (24, 25).
The most significant change in gene expression within tumors is tumor-
related genes, and such a change in expression profiles may lead to
different radiation responses. Thus, we only performed a cancer-
related gene array in this study. Sixty genes of 1187 were determined
to be prognostic genes for radiation response based on two criteria: (a)
the ratio of gene expression between radiation-resistant and -sensitive
samples was >3-fold; and (b) the absolute difference was >75, if the
ratio was undefined during the analysis. Interestingly, these genes
included some of the classically known radiation-responsive genes
such as c-jun and XRCC1, but many genes listed in Table 1 have not
been tested in the literature. The cluster analysis enabled us to orga-
nize these 60 genes into three categories: (a) a group with undetect-
able gene expression in a radiation-resistant sample and relatively
high level of gene expression in radiation sensitive samples (with an
absolute expression difference of >75); (b) a group with genes over-
expressed in a radiation-resistant sample; and (c) a group with genes
overexpressed in radiation-sensitive tissues. The last two groups had
gene expression ratios >3-fold. Interestingly, this selection of 60
genomes enabled us to successfully predict two testing samples (Fig. 3).

Although two predictions do not confer statistical significance, our
goal is to provide a novel alternative approach to predict the radiation
response. We emphasize here that this technique aims to determine
radiation response in pretreatment based on the expression of identi-
\fified genes by array (Tables 1 and 2), which is a determination of a
genome-based change that occurs in tumors and accounts for the differ-
ential radiation response. As such, this approach did not consider the
expression of radiation-inducible genes that also affect the radiation
response. It is our future plan to polish this approach, and we will
explore other genes that should be included in this gene pool to predict
the radiation outcome.

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Expression of bcl-2 protein predicts efficacy of adjuvant treatments in operable
protein expression correlates with recurrence and survival in early stage head and


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